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EFFECT OF ADRENALIN ON THE TEMPERATURE OF SKELETAL MUSCLE BEFORE AND AFTER LIGATION OF THE HEPATIC ARTERY AND THE PORTAL VEIN

DISSERTATION

PRESENTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE GRADUATE SCHOOL OF THE OHIO STATE UNIVERSITY

BY

MARION WILLIAM CASKEY, B.A., M.A.

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PREFACE

This study is an attempt to show whether removal of the liver from the circulation is actually followed by a marked alteration in the temperature reaction of the body to adrenalin.

The work was prompted by the researches of Boothby and Sandiford on the calorigenic action of adrenalin, by the observations of Crile and Rowland on the effect of adrenalin on the temperature of animal tissues and by some earlier work of Caskey and Spencer on the effect of adrenalin on the brain temperature of dogs.

The writer wishes to express his appreciation to Professors R. C. Osburn and R. G. Hoskins for their interest in and direction of this work and to Professor Hoskins for laboratory facilities for the experiments.

M. W. C.

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Reprinted from THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 80, No. 2, April, 1927

EFFECT OF ADRENALIN ON THE TEMPERATURE OF SKELETAL MUSCLE BEFORE AND AFTER LIGATION OF THE HEPATIC ARTERY AND THE PORTAL VEIN

M. W. CASKEY

From the Ohio State University

Received for publication November 8, 1926

Crile and Rowland (1922) reported experiments on rabbits which indicate that the injection of adrenalin chloride is followed by an increase of brain temperature. They reported that adrenalin injection after hepatectomy is not followed by an increase of brain temperature. They also reported that the temperature of skeletal muscle is not affected by adrenalin injection either before or after hepatectomy. Caskey and Spencer (1925), working on dogs, confirmed some of these findings. They found that there was an increase in the temperature of the brain and skeletal muscle following the intravenous injection of adrenalin. Their data throw some doubt on Crile and Rowland's suggestion that the brain reacts thus peculiarly to adrenalin. Since there is heat produced in other parts of the body during the period of adrenalin stimulation, an increase in brain temperature could with difficulty be ascribed to reactions occurring in the brain alone. It must be remembered that in all of these experiments the brain was in circulatory connection with the muscles and other body tissues. Since a different type of animal was used by Caskey and Spencer, it is evident that their results are not necessarily at variance with those of Crile and Rowland.

In continuation of these investigations on dogs, it was decided to study the effect of adrenalin on body temperature before and after removal of the liver from the circulation. The liver is an important factor in the carbohydrate metabolism of the body. Adrenalin stimulates the liver and the liver responds by suddenly discharging an excess of sugar into the blood stream. The work of Collens, Shelling and Byron (1926) shows that adrenalin is unable to produce this normal hyperglycemia when the hepatic artery has been ligated previous to the injection of the drug. The longer the time elapsing between ligation and injection of adrenalin, the less the increase in blood sugar.

The work of Boothby and Sandiford (1920, 1921, 1923) and Sandiford (1920) shows that body metabolism is definitely stimulated by the injection of adrenalin into the body, but that this stimulation is more probably

due to a specific dynamic effect rather than solely to an increase of carbohydrate available for metabolism.

In view of these facts and the interesting observations of Crile and Rowland, it seemed wise to employ liver extirpation as part of the method for studying the problem of the adrenalin heat reaction. It was expected that the data of this study should show whether the removal of the liver from the circulation is actually followed by marked alteration in the temperature reaction of the body to adrenalin. The data should likewise give some idea of the causes of the increased body temperature which follows adrenalin injection. The accompanying blood-pressure records, for example, should indicate whether the temperature changes are to be interpreted in terms of circulatory changes. The course of the temperature during the whole experiment might also suggest whether the adrenalin heat variations are due to variations in the functioning of the heat regulatory mechanism.

Methods. Dogs of both sexes and of varying weights were used. The animals were anesthetized with ether, barbital or a combination of the two.

The thermocouple was selected as a means of measuring directly the rate and amount of temperature change. Since changes of less than 0.01°C. were not regarded as significant in these experiments, a single copper-"constantine" couple was employed. One copper-"constantine" junction was placed in a thermos bottle filled with water and equipped with a thermometer. The other junction was embedded in the tissue, the temperature of which was to be recorded. A Leeds and Northrup d'Arsonval galvanometer was connected in the thermocouple circuit at the beginning of an experiment and its deflections were recorded during the course of the observations.

The deflections of the galvanometer coil for known differences in temperature of the copper-"constantine" junctions were observed. The calibration of the apparatus was based on these observations. The actual temperature of the structure being studied was determined by translating galvanometer deflections in terms of degrees centigrade and adding this figure to the temperature of the standard thermos bottle in which the reference junction was located.

In the course of a given experiment there was an average fall of 0.005°C. per minute in the temperature of the standard thermos bottle. This change was so small in proportion to the temperature fluctuations of the tissues studied that it seemed unnecessary to maintain the reference couple at a rigidly constant temperature. However, a correction formula was applied to all galvanometer readings. These readings were taken every ten seconds during the early stages of each experiment and every thirty seconds during the later stages.

In order to use the thermocouple it was necessary to select some location in the body which *a*, responds readily to temperature changes in the body; *b*, is of similar temperature to the remainder of the body; *c*, and is influenced proportionately to the rest of the body by temperature changes.

Finding the most desirable place for thermocouple implantation necessitated a number of preliminary experiments. These showed in brief that a marked increase in the temperature of the blood, viscera and skeletal muscles follows adrenalin injection. It was found that the average temperature change in skeletal muscle was equal to that observed in the loops of the small intestine and comparable to that found in the blood. These changes could be followed accurately in skeletal muscle. There, the technique of implantation was easy and the trauma incident to it was slight. The thermocouple was placed beneath the vastus medialis muscle or between the pectoralis major and the pectoralis minor. The same type of results was obtained in either location.

Several methods of removing the liver from the circulation were considered: *a*, by Eck fistula; *b*, by ligation of the hepatic artery and the portal vein; *c*, by ligation of the hepatic vein. The Eck fistula would have obviously had some advantages over the ligation of the hepatic artery and the portal vein had the determinations stretched over a period of several hours. But since they were begun in three to five minutes after ligation, the trauma of the Eck fistula technique presumably would have been more deleterious than the stagnation of the blood occurring in the viscera in the three to five minutes before the determinations which followed, were begun. Ligation of the hepatic vein in such manner as not to interfere with the vena cava would have been accompanied by much trauma. The introduction of two fingers into the abdominal cavity and the passing of a ligature around the hepatic artery and the portal vein required a minimum amount of manipulation of the viscera. In most cases, ligatures were laid at the beginning of the experiment but in no case did they inhibit the adrenalin heat effect until they were later tied. In eleven preliminary experiments, ligation of the hepatic artery and the portal vein excluded the liver satisfactorily and incidentally the adrenalin phenomena observed were comparable in every way to those observed in the later experiments.

The technique for liver exclusion might be criticized, for by it the pancreas is removed from the circulation. Since the pancreas plays such an important rôle in carbohydrate metabolism, its removal along with the liver might give distinctly different effects from that following simple hepatectomy. Mann and Magath (1923) have shown, however, that when the pancreas and liver are both removed at the same operation the resultant condition in general is the same as if only the liver had been removed. They were interested primarily in changes of blood sugar.

Moreover, they report that after such an operation the injection of glucose restores the animal to normal. This indicates that the experimental animal metabolizes carbohydrates in the absence of the pancreas.

It seemed possible that removing such a large part of the organism from the circulation might alter the speed and extent of the general distribution of adrenalin through the parts of the animal yet in the blood circuit. Accordingly, the blood pressure was recorded from the left carotid artery. It was with this as a standard that we hoped to compare rate and amount of activity of adrenalin before and after ligation.

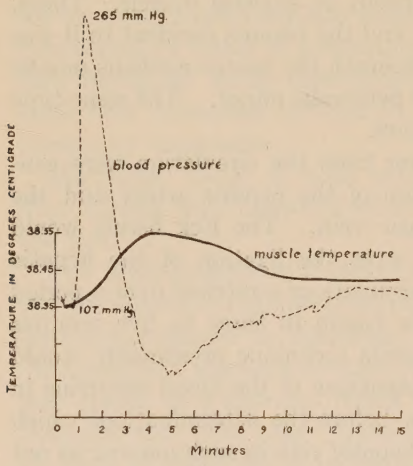

Fig. 1

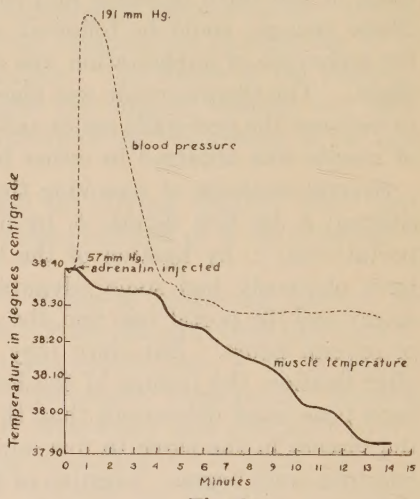

Fig. 2

Fig. 1. Blood pressure and muscle temperature before ligation of the hepatic artery and the portal vein (arrow denotes adrenalin injected).

Fig. 2. Blood pressure and muscle temperature after ligation of the hepatic artery and the portal vein.

After this preliminary standardization of methods, the following program was carried out:

a. The animal was anesthetized with barbital or ether, or a combination of both.

b. The carotid artery was exposed and connected with the mercury manometer arranged to record the blood pressure.

c. The thermocouple was inserted in a muscle bed.

d. The basilic vein was exposed and prepared for adrenalin injection.

e. The abdomen was opened and ligatures passed but not tied about the hepatic artery and the portal vein.

f. Galvanometer readings were taken to determine the stability of the temperature of the animal thus prepared.

g. Adrenalin was injected and the temperature changes were recorded.

h. The ligatures, previously placed, were tied about the hepatic artery and the portal vein. The vessels were included in the same ligatures and were not tied separately.

i. Adrenalin was injected and the temperature changes were recorded.

Several pre-ligation and post-ligation determinations were made on each of fifteen experimental animals. Table 1 summarizes six representative experiments. A typical pre-ligation and post-ligation observation is shown in each instance.

Observations. There was in general a fall in muscle temperature during the course of each experiment. This fall was changed temporarily to a rise if adrenalin was injected intravenously. The character of these rises is indicated in figure 1. The amount and time relations of typical rises are shown in table 1. Adrenalin injection resulted in considerable variation in increase of temperature in different animals. The highest rise observed was 0.37°C. The next highest was 0.24°C. The other rises graded down to 0.07°C., though the majority were between 0.10°C. and 0.20°C. In many cases the muscle temperature after having risen, did not return to normal during any given determination (a period of ten to fifteen minutes).

After the liver was excluded from the circulation, the muscle temperature continued to fall, but at a much more rapid rate. Adrenalin injection after hepatectomy caused only infrequent and small transitory rises. In two cases after ligation of the hepatic artery and the portal vein, there was a rise of 0.02°C. and in one case, a rise of 0.01°C. In all other post-ligation determinations there was no rise but a rather marked fall after ligation. When the above small rises did occur, they did so within one minute and ten seconds after the injection of adrenalin. The maximal rise before ligation required an average of six minutes after the injection of adrenalin. The return to normal of these three small rises occurred much more rapidly than did the return of the pre-ligation rises.

The general features of the blood pressure and its relation to the muscle temperature are shown in figures 1 and 2.

Discussion of data. A considerable variation was noted in the amount of temperature increase which followed the injection of adrenalin in various pre-ligation determinations. There are a number of factors which cause such variations. These factors include: (*a*), room temperature; (*b*), general physiological condition of the animal; (*c*), amount of adrenalin injected; (*d*), time elapsing between injections; (*e*), time elapsing between placing the animal on the table and the first adrenalin injection; (*f*), such individual variations as hair length, ratio of total mass to total surface area of the body, and differing susceptibility to adrenalin.

In general, the larger the dose of adrenalin, the greater was the response

TABLE 1

Showing the effect of the intravenous injection of adrenalin on muscle temperature and blood pressure before and after ligation of the hepatic artery and the portal vein

EXPERIMENT NUMBER	WEIGHT OF DOG	SEX	ANESTHETIC	DOSAGE OF ADRENALIN PER KGM. BODY WEIGHT	TEMPERATURE IN MUSCLE AT BEGINNING OF RECORD	MAXIMAL RISE IN TEMPERATURE OF MUSCLE ABOVE INITIAL TEMPERATURE	TIME INTERVAL BETWEEN INJECTION OF ADRENALIN AND MAXIMAL TEMPERATURE OF MUSCLE	INITIAL BLOOD PRESSURE	MAXIMAL RISE IN BLOOD PRESSURE ABOVE INITIAL	TIME INTERVAL BETWEEN INJECTION OF ADRENALIN AND HIGHEST BLOOD PRESSURE	FIRST MAJOR FALL IN BLOOD PRESSURE BELOW INITIAL	TIME INTERVAL BETWEEN INJECTION OF ADRENALIN AND LOWEST BLOOD PRESSURE
	kgm.				°C.	°C.		*mm.* Hg.	*mm.* Hg.		*mm.* Hg	
1 A	14.4	M.	Barbital 60 grains	0.0354	36.90	0.13	5′ 30″	145	142	1′ 20″	6.00	4′ 20″
B*				0.0354	36.55	0.00		130	126	50″	20.00	3′ 20″
2 A	15.3	M.	Barbital, 62.5 grains	0.0326	37.1	0.10	4′ 40″	122	90	50″	16.00	6′ 0″
B*				0.0326	37.3	0.00		70	80	1′ 0″	10.00	7′ 30″
3 A	17.0	M.	Barbital, 70 grains	0.0352	38.35	0.20	4′ 10″	107	158	1′ 20″	38.00	4′ 50″
B*				0.0352	38.4	0.00		63	134	1′ 0″	28.00	6′ 50″
4 A	9.5	M.	Barbital, 38 grains	0.0421	38.4	0.10	5′ 40″	110	76	1′ 0″	46.00	3′ 0″
B				0.0421	38.35	0.15	13′ 10″	110	70	40″	44.00	3′ 10″
C*				0.0631	38.47	0.00		52	70	1′ 10″	40.00	6′ 0″
5 A	24.0	M.	Barbital, 97.5 grains	0.0316	39.2	0.17	13′ 0″	154	130	40″	32.00	3′ 50″
B*				0.0316	39.45	0.00		90	174	1′ 10″	30.00	6′ 40″
6 A	11.6	M.	Barbital, 50 grains	0.0344	37.10	0.23	12′ 50″	75	96	30″	24.00	6′ 0″
B*				0.0344	37.41	0.00		65	70	1′ 0″	24.00	5′ 0″

* The hepatic artery and the portal vein were ligated.

of the animal to it. Individual variations, however, are often responsible for greater differences in adrenalin response than are moderate differences in doses. To my knowledge, this has not been fully explained. A varying susceptibility was frequently noted and in two cases it was necessary to vary the standard dosage to get an optimum response.

In spite of the variable factors, and perhaps others not recognized, the results are fundamentally the same in all experiments, i.e., the injection of adrenalin is followed by an increase in the temperature of skeletal muscle, provided that the liver circulation is intact.

Since the adrenalin temperature changes observed previous to hepatectomy were usually superimposed on a falling muscle temperature, it is evident that the rises observed were in reality slightly less than the actual temperature increases.

The conclusion that adrenalin does not increase muscle temperature if injected after hepatectomy is based on the fact that no increase in muscle temperature is observed under these conditions. But since the muscle temperature fell steadily after hepatectomy, it might be argued that the fall was large enough to conceal any temperature increase which might have occurred after the injection of adrenalin. It should be noted, however, that in the hepatectomized animal the average fall in temperature during the first five minutes following adrenalin injection was 0.126°C.; during the second five minutes it was 0.102°C. Evidently, adrenalin caused no temperature increase during the first five minutes. If any increase did occur during the second five minutes, it was negligible. In the pre-ligation experiments, the peak of the heat reaction is usually reached during the first five minutes after the injection of adrenalin. That the first five minutes should likewise be the critical period in the post-ligation determinations seems evident since the rise in blood pressure was comparable in speed and amplitude to the pre-ligation changes. Since most of the abdominal viscera were removed from the circulation in the post-ligation determinations, the blood-pressure response indicates a responsive circulatory system in the muscles, the site of temperature observations.

The full significance of the observation, that the peak of the pressor response to adrenalin is passed before the heat reaction is well under way, has not been investigated in these experiments. These observations suggest that the heat reaction is not attributable alone to the shifting of warmer blood from the viscera to the muscles. It will be remembered that adrenalin in pressor doses causes a flooding of the blood vessels of the skeletal muscles along with mass shifting of blood from the viscera to the muscles. Since the peak of the blood pressure elevation is reached before the heat reaction is well under way, it would seem that the larger part of this shifting is over before the temperature elevation is well begun.

These observations indicate that the pressor response and the elevation of temperature are only parallel reactions and are not interdependent. This last conclusion is borne out by the observations following the ligation of the liver vessels.

Interpretation of results. It is clear that removal of the liver by the method employed prevents the normal increase in muscle temperature which follows adrenalin injection. Some suggestions are offered as to why the hepatectomized animal reacts as it does following the injection of adrenalin. It must be remembered that the animal was in a state of surgical anesthesia and to that extent, at least, was not reacting normally. Anesthesia, the major operation, and placing and tying the ligatures produce more or less profound systemic disturbances. As a control measure, the animal was usually operated upon and the ligatures placed (not tied) around the hepatic artery and the portal vein, before any adrenalin was injected. In animals thus prepared adrenalin invariably caused a rise in muscle temperature. The view that the observed phenomena are not due to surgical or traumatic shock is substantiated by some later experiments performed by the writer in the Laboratory of Physiology and Pharmacology of the University of Louisville and reported in abstract in the Proceedings of the American Physiological Society, December 1925. It was observed in these experiments that adrenalin caused an increase in muscle temperature after the venous blood supply to the liver was cut off. In these observations it was noted that the blood pressure fell just as low following removal of part of the liver circulation as it did following the removal of all of the liver circulation in the earlier experiments.

Of the various disturbances which follow hepatectomy, there are two which, operating singly or in combination, are sufficient to account for the failure of the muscle temperature to increase following the injection of adrenalin, i.e., changes in carbohydrate metabolism and change in blood concentration.

It is known that the liver responds to adrenalin by a large rapid discharge of sugars. The removal of this organ which stores about one half of the body carbohydrate, glycogen, would profoundly affect the oxidative processes in the body. Claude Bernard (1855, 1877) showed that the liver contains a substance which converts starch to sugar. It is possible that the liver may also supply some active principle hastening the formation of sugar from glycogen stored in the other tissues of the body.

Lamson and others (1915, 1916, 1920, 1921, 1923) have shown that the liver responds to the intravenous injection of adrenalin by concentrating the blood. As has been pointed out by Barbour (1921), blood concentration is followed by a reduction in the rate of loss of body heat. A slower rate of heat loss from the body would be followed by an increase in muscle temperature provided that the general body metabolism did not decrease

and that the circulation to the muscles were not impaired. The work of Boothby and Sandiford shows that adrenalin causes an increase in body metabolism, and the work of Hoskins, Gunning and Berry (1916) has shown that adrenalin causes a vasodilatation in the muscles and vasoconstriction in the skin.

CONCLUSIONS

From the experiments of other workers it seems clear that: *a*, an increased amount of carbohydrate in the blood contributes to the normal increase of body heat following the injection of adrenalin; *b*, that this carbohydrate increase is due principally to the liver; *c*, that in the absence of the liver, adrenalin is incapable of producing hyperglycemia; *d*, that the liver functions as a blood concentrating organ after the intravenous injection of adrenalin.

From the results of the present experiments it seems clear that: *a*, the adrenalin pressor reaction is not interfered with materially by the stopping of the adrenalin heat reaction—hence that the two reactions are relatively independent; *b*, that the phenomena observed after total removal of the liver from the circulation are not due to "surgical shock" or other experimental conditions, but are due to removal of the liver as a functional factor in the adrenalin temperature rise; *c*, that removing the liver from the circulation prevents the usual increase in temperature of skeletal muscle of anesthetized dogs after intravenous injection of adrenalin. This failure of temperature increase may be due to: *a*, removal of an organ which when stimulated by adrenalin mobilizes an excess of readily metabolizable carbohydrate from within the liver itself or possibly from elsewhere in the body through the agency of some liver secretion, producing glycogenolysis; *b*, removal of a blood concentrating organ which would (as suggested above) by removal of fluid from the blood, place a lower limit on the amount of heat loss occurring from radiation, evaporation, and other physical means by which heat is lost from the surface of a body.

The writer wishes to express his appreciation to Professors R. C. Osburn and R. G. Hoskins for their interest in and direction of this work, and to Professor Hoskins for laboratory facilities for the experiments.

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AUTOBIOGRAPHY

I, Marion William Caskey, was born at Salado, Texas, June 24, 1900. I received my secondary school education in the public and high schools of the city of Waco, Texas. I entered Baylor University at Waco, Texas, in 1918 and received the B.A. degree in 1921. The following year I was University Fellow in Zoology. I received the M.A. degree from Baylor in 1922. In 1922–23 I was instructor in Zoology there. From 1923–25 I pursued graduate studies at the Ohio State University, holding first a University Scholarship and later a University Fellowship in Zoology. I received the degree of Doctor of Philosophy from this institution in June, 1925.